Pediatr Transplantation 2005: 9 (Suppl. 7): 81–86

Pediatric Transplantation

Fanconi's Anemia, transplantation, and cancer

Alter BP. Fanconi's anemia, transplantation, and cancer. Pediatr Transplantation 2005: 9 (Suppl. 7): 81–86. © 2005 Blackwell Munksgaard

Abstract: Patients with Fanconi's Anemia (FA) have high rates of congenital physical abnormalities, bone marrow failure, leukemia, and solid tumors. Stem cell transplant (SCT) is often effective in curing bone marrow failure, but high-risk patients, particularly those whose donor is not a human leukocyte antigen matched sibling, are vulnerable to early mortality from transplant-related complications. Long-term survivors of SCT have risks of solid tumors (particularly of the oral cavity), which are even higher than the already high 'baseline' risk of neoplasia in untransplanted FA patients. In this group, the major types of cancer are head and neck squamous cell carcinomas, and gynecologic malignancies. Rapid evaluation of new SCT preparative regimens would be useful in improving both short-term and long-term results.

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Key words: Fanconi's anemia – bone marrow transplant – cancer – leukemia – aplastic anemia

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FA is a recessive disorder in which the majority of the known patients have characteristic birth defects, a high rate of development of aplastic anemia, and high risks of leukemia and solid tumors (1, 2). A hallmark is chromosomal instability, associated with defective repair of DNA damage (3). More than 11 genes are involved in the FA pathway; mutations in ten of these are inherited as autosomal recessives, while one, *FANCB*, is X-linked recessive (4, 5). Although most of the FA genes are novel, *FANCD1* is *BRCA2* (6). The products of the FA genes function in a pathway, which is activated following DNA damage. The FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, and FANCL proteins form a complex, which is required for ubiquitination of the FANCD2 protein. Ubiquitinated D2 apparently interacts with FANCD1/BRCA2 and then co-localizes with other proteins in DNA damage-response foci (including BRCA1, Rad50, Mre11, NBS1, etc) (7).

Abbreviations: AML, acute myeloid leukemia; BMT, bone marrow transplant; CI, confidence intervals; FA, Fanconi's Anemia; HLA, human leukocyte antigen; HNSCC, head and neck squamous cell carcinoma; MDS, myelodysplastic syndrome; NAS, North American Survey; SCC, squamous cell carcinoma; SCT, stem cell transplant; SLH, Hôpital Saint Louis.

The clinical manifestations of FA are heterogeneous, ranging from multiple birth defects to completely normal appearance (8). Since the latter may occur in ~25% of patients with FA, this diagnosis must be ruled out in all children with aplastic anemia. The patients with early onset hematologic disease tend to be those with the more severe physical phenotype, but this is by no means a perfect correlation (9, 10). The risks of leukemia and solid tumors are very high in FA and are more likely in those patients who did not develop early onset bone marrow failure. These risks of neoplastic disease are not eliminated in patients who receive a stem cell transplant, and it appears that they may be increased following this procedure.

This review provides a summary of the major adverse outcomes in patients with FA, indications for SCT, complications of SCT in these patients, and speculation with regard to how the results of SCT might be improved.

Methods

Published data for this review were obtained by searching the medical literature using Medline, supplemented after reviewing the bibliographies of each publication. The search terms were 'Fanconi's Anemia', or 'aplastic anemia'. Original data were obtained from the author's North American Survey. Detailed results from all of these endeavors have been published previously (1, 8, 10–12).

Results and discussion

The cumulative risk of major complications in cases from the medical literature was examined using standard Kaplan–Meier survival analyses. The risk of severe aplastic anemia was ~90% by age 50, AML 40% by age 30, MDS 50% by age 45, liver tumors 45% by age 50, and solid tumors 75% by age 45 yr (8). These standard survival analyses make the assumption that the patients are at risk of only the complication being analyzed. However, competing risk analytic methods provide the cumulative risk of any adverse event in the presence of other outcomes. With this approach, the cumulative incidences of severe marrow failure, leukemia, and solid tumors are 52, 10, and 29%, respectively (see later for further details).

Most cancers in the general population occur in older individuals, at a median age of 68 yr. In the literature reports of more than 200 FA patients, however, cancer developed significantly earlier, at a median of 16 yr of age for all sites, 26 for all solid tumors, and 14 for leukemia (Table 1) (1). Half of the cancers were AML, and the majority of the others were liver tumors [adenomas and hepatocellular carcinomas (13)], HNSCCs, esophageal tumors, and gynecologic cancers (vulva, vagina, and cervix). One hundred cancers were reported in 86 patients. One male had two and another had four cancers. Five females had two, one had three, and one had four malignancies. Thirty-eight FA patients who had not received a SCT had head and neck cancer at a median age of 26 yr, while 13 who had received an SCT developed oral cancer at a younger median age of 21 yr ($p = 0.02$). This literature review thus indicates that the risk of malignancy is very high in FA and that it might be even higher following SCT.

A survey of North American patients with FA, which was performed in 1999–2000, provided information about outcomes that could be analyzed more completely than the literature reports (10, 11). Among 145 respondents to 318 surveys (Table 2) there were 14 subjects who had 18 tumors, 9 individuals with AML, and 23 with MDS (which was not considered to be a malignancy) (14). The most significant observation was that the patients who reported solid tumors were diagnosed as FA at an older age (median 7.6 yr) than those with AML or no cancer (medians 3.8 and 4.6 yr). This suggested that those who developed solid tumors were clinically less severe than those who did not develop tumors.

The number of FA respondents who reported cancer or leukemia was much larger than expected for a normal population of the same age, sex, and birth cohort (15) (Table 3). The ratio of that observed in FA to that expected in the general population was 50 for all cancers, and 48 for solid tumors. Leukemia and head and neck cancer were reported at >700 times the expected rate, and vulvar and esophageal cancers at >4000 and >2000-fold respectively. The relative rates for these specific cancers were very high in the patients with FA because they are cancers not usually seen in the FA age group. These increased rates were highly significant, confirming

Table 1. Median ages (years) for cancer in the FA literature, 1927–2001

Cancer	General age	FA age*	FA range	FA no.
All sites	68	16	0.1–48	211
All solid tumors	–	26	0.2–45	68
Leukemia (AML)	68	14	0.1–29	116
Liver	68	13	6–48	37
Head and neck				
No BMT	64	28	13–41	38
After BMT		21†	11–33	13
Esophagus	68	27	20–36	9
Vulva/anus	72	27	20–37	10
Cervix	47	25	22–32	3
Brain	56	3	0.5–11	6
Breast	63	37	26–45	4

AML, acute myelocytic leukemia; BMT, bone marrow transplant; FA, Fanconi anemia.
*~1300 FA patients in literature, 1927–2001. General population data from the Surveillance, Epidemiology, and End Results (SEER) program (15).
†Only these patients received a BMT. $p = 0.02$ for median age compared with FA patients with head and neck cancer who had not received a BMT. Adapted from Ref. 1.

Table 2. Demographics of North American survey respondents with FA

Parameter	Total	Solid tumor	Leukemia	MDS*	No cancer
Number	145	14†	9	23	122
Male:female	76:69	6:8‡ 6:6‡	6:3	17:6	64:58
Median age at FA diagnosis§	4.8 (0–45)	7.6 (0.09–45)¶	3.8 (0–11)	5.3 (0–41)	4.6 (0–41)
Median age at outcome§	NA	28.9 (7–45)	11.3 (3–24)	12.3 (2–41)	NA

FA, Fanconi anemia; MDS, myelodysplastic syndrome; NA, not applicable.
*MDS was not considered to be a malignancy.
†14 individuals had 18 tumors: six head and neck cancers, two each of esophageal, liver, and cervix cancers, three vulvar cancers, and one each of osteosarcoma, soft-tissue sarcoma, and brain cancer. None reported either breast or ovary cancer.
‡Male to female ratio before and after exclusion of two women with only gynecologic cancers.
§Age = years (range).
¶$p < 0.01$ by chi-square, compared to those without solid tumor.
127/284 from USA, 18/34 from Canada. Adapted from Ref. 11.

Table 3. Observed cancers, ratio of observed to expected cancers, and 95% CIs among North American respondents with FA

Type	Observed*	O/E†	95% CI‡
Total cancers	27	50§	35–80
Total solid tumors	18	48§	30–80
Leukemia (AML)	9	785§	360–1490
Head and neck	6	706§	260–1540
Esophagus	2	2362§	265–8530
Liver	2	386§	45–1395
Vulva	3	4317§	870–12615
Cervix	2	179§	20–645
Osteosarcoma	1	79	1–440
Soft-tissue sarcoma	1	49	0.6–270
Brain	1	17	0.2–95

AML, acute myelocytic leukemia; CI, confidence intervals.
*A total of 27 cancers observed in 23 patients. Two patients had two solid tumors (cervix and vulva, and vulva and esophagus) and one patient had three solid tumors (esophagus, liver, and cervix).
†Observed/expected, expected cancer incidence rates adjusted for age, sex and birth cohort, calculated from the Connecticut Tumor Registry.
‡Limits of the 95% CI rounded to the nearest five for values greater than or equal to 10.
§$p < 0.05$ that true O/E ratio equals 1.0, using exact 2-sided tests. From Ref. 11.

and quantifying the prior impression that FA is a highly premalignant disorder.

Analyses of conditions with multiple outcomes are most appropriately performed with competing risks methodology, in which the first event precludes any other event being 'first'. In the context of FA, the initial adverse events are death (without SCT) or SCT, both related to severe bone marrow failure; AML; or a solid tumor (Fig. 1). The annual hazard rates for these outcomes in the NAS are shown in Fig. 2a. The rate of BMT reached a maximum of 4% per year by age 7, and then declined to about 1% per year by age 20. The hazards of AML and of death from bone marrow failure rose during childhood, peaked at around 1% per year in teen years, and then appeared to level off or decrease during early adulthood. The most interesting pattern is that of solid tumors, which were very low in early childhood, but then rose in a more than linear manner, reaching 4% per year by age 30 yr, and around 10% per year by age 45.

Figure 2b shows the cumulative incidence of each of these major adverse events. More than 30% of the FA respondents had a BMT by age

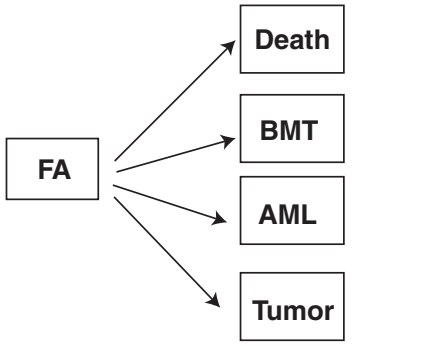

Fig. 1. First adverse events in FA, by competing risks. *Death* is from aplastic anemia. *BMT* indicates bone marrow transplant because of severe aplastic anemia. *AML* is acute myeloid leukemia as the first event. *Tumor* indicates solid tumor as the first event. Patients were censored at the time of their first event.

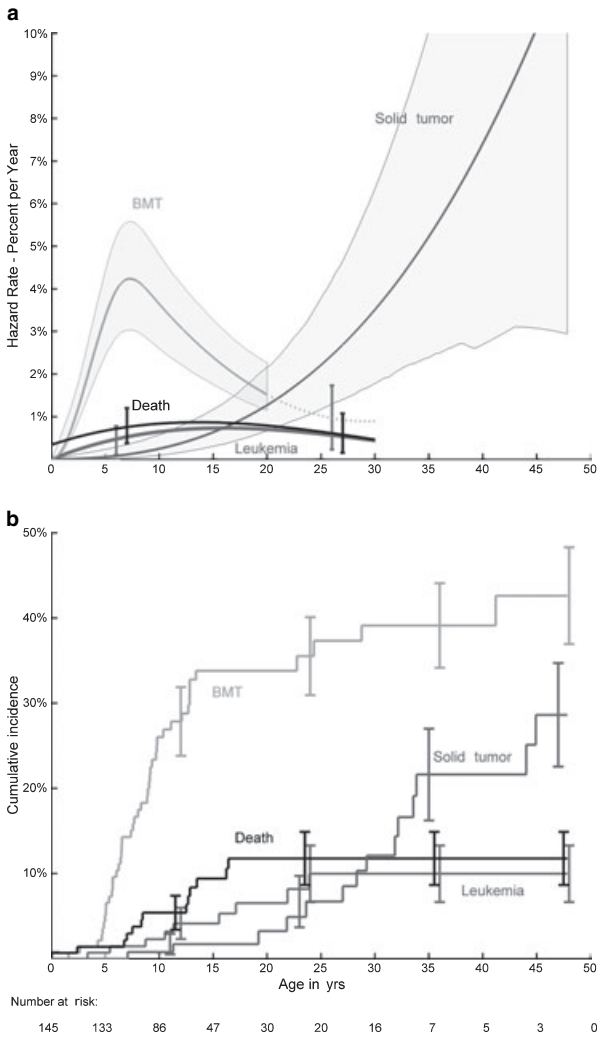

Fig. 2. Annual hazard rates and cumulative incidence of cancer in FA by age. (a) Annual hazard rates (incidence rate per year among subjects who are still susceptible) of death, BMT, AML, and solid tumor, and 95% point-wise confidence envelopes (shaded regions) or intervals at selected years (error bars). (b) Cumulative incidence by age (cumulative percent experiencing each event as initial cause of failure) and 95% CIs at selected years (error bars). The number at risk of an event is shown below the age axis. From Ref. 11.

13, and 40% by age 45 yr. By age 17, 12% had died from hematologic complications, and no further deaths from this cause were reported in older patients. The cumulative incidence of AML reached its maximum of 10% by age 24 yr. The cumulative incidence of a solid tumor was below 2% until the 20s, after which it increased to 9% by age 28, and 29% by age 48 yr, without appearing to reach a plateau. The results indicate that the major risk to the older FA patient who does not have the earlier complications of bone marrow failure or leukemia is a solid tumor, particularly HNSCC, esophageal cancer, and gynecologic tumors. It is important to emphasize that this analysis involved competing risks in which only one event could be the first adverse event. Certainly patients with FA who survive early hematologic complications are also at risk of subsequent solid tumors, but the incidence of secondary adverse events was not examined in this analysis.

The consensus guidelines for treatment of hematologic complications in patients with FA are summarized in the Standards for Clinical Care (16): cytopenias with Hb <8 g/dL or symptoms, platelets $<30\,000$ per mm^3, absolute neutrophil count <500 per mm^3; leukemia; or MDS with cytopenias and morphologic marrow changes, and not for cytogenetic clones without impact on marrow function. The current treatment choices include SCT, androgens, and hematopoietic growth factors, and gene therapy trials are beginning to accrue patients. While gene-corrected marrow cells may outgrow uncorrected cells, one major concern is that residual uncorrected stem cells may continue to reside in the patient's bone marrow, and thus the risk of MDS or AML will remain.

A comparison of the survival curves for transplanted and untransplanted patients with FA from the NAS is shown in Fig. 3. At first glance, it appears that patients who were not transplanted did better than those who did receive a transplant. However, this is actually a good example of 'confounding by indication,' in which the group who received an SCT were more likely to die without the transplant, and those who did not receive an SCT were less severely affected.

As mentioned above, patients with FA who survive a SCT may be at an increased risk of solid tumors. Fourteen such cases were reported in the literature (Table 4) (1, 17, 18), including nine males and five females, and all tumors were in the oral cavity. The age at transplant ranged from 6 to 20, the age at cancer was from 11 to 34, and the interval

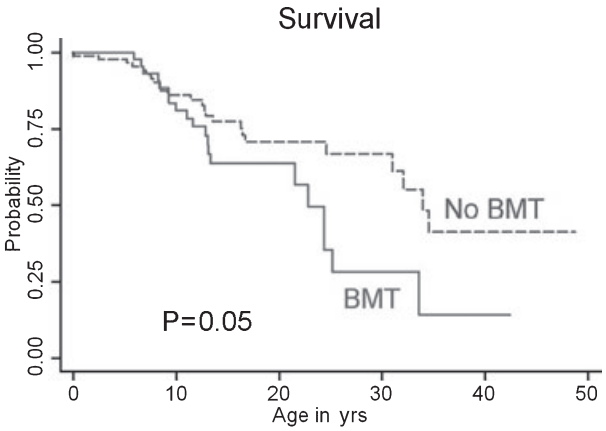

Fig. 3. Kaplan–Meier survival curves of patients with FA who did (solid line) or did not (dashed line) receive a BMT. Data are from the North American Survey. Patients who received a BMT had a median survival age of 24 yr; for those without BMT the median survival was 34 yr. This is 'confounding by indication' – those who received a BMT were unlikely to have survived without the procedure.

Table 4. Tumors after bone marrow transplant, reported in the literature

No	BMT age (yr)	Gender	Cancer age (yr)	Cancer type	Interval (yr)	Result	Age (yr)
1	20	F	25, 29	Cheek, tongue	5, 9	D	30
2	14	F	24	Tongue	10	A	32
3	9	F	18	Buccal	9	D	18
4	9	F	23, 24	Vulva, tongue	14, 15	A	25
5	6	M	12	Tongue	6	D	12
6	8	M	11	Tongue	3	D	11
7	8	M	16	Tongue	8	A	16
8	19	M	33	Tongue	14	D	33
9	NA	M	NA	Tongue	5	A	NA
10	8	M	13	Tongue	5	D	13
11	10	M	25	Pharynx	15	D	25
12	–	M	19	Tongue	NA	D	19
13	–	F	34	Larynx	21	A	34
14	7	M	9	Tongue	2	A	11

A, alive; BMT, bone marrow transplant; D, deceased; F, female; M, male; NA, not available.
Updated from Ref. 1 with the addition of Refs. 17 and 18.

from BMT to cancer was from 2 to 15 yr. Nine patients died within the year that they developed cancer, and reported follow-up was short for most of those who were surviving.

In order to better quantify the additive risk of cancer imparted by BMT, outcomes were compared between 117 FA patients who received a BMT at the SLH in Paris, and 145 patients in the NAS who were not transplanted or were censored at BMT (12). The Paris data include patients who were transplanted from 1976 to 2002, and followed through 2003. Although transplant modalities have evolved since then, this group comprises a large cohort in which the

majority of the patients were treated with a similar protocol, based on cyclophosphamide and irradiation; details are provided in the cited publication. There were 11 patients with HNSCC among 508 person-years in the transplanted group, and seven among 1983 person-years in the untransplanted cohort; the respective median ages were 19 and 33 yr ($p = 0.004$). Transplant increased the age-specific risk of HNSCC by 4.4-fold and shifted the median age by 16 yr, from 45 to 29 yr (Fig. 4).

There was a high rate of early deaths post-transplant, with a cumulative incidence of 35% by 6 months after the procedure (Fig. 5). Many factors were examined with regard to their association with early non-SCC death or development of SCC. After adjustment for multiple comparisons, significant associations with early deaths included treatment factors (antithymocyte globulin, cyclosporine, busulphan, total lymphoid irradiation at 5 Gy), host factors (acute graft vs. host disease and age at transplant above the median of 10.8 yr), and alternative donors. For SCC, however, the only significant associations were acute graft vs. host disease (relative hazard 33-fold) and chronic graft vs. host disease (present in all 11 of the patients with HNSCC). Specifically, there was no significant association of SCC with prior use of radiation or cyclophosphamide.

Challenges with regard to SCT in FA are the development of transplant protocols that reduce

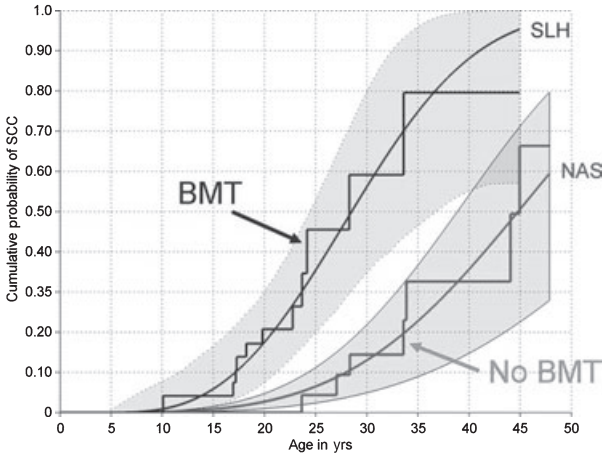

Fig. 4. Hypothetical cumulative incidence curves for SCC in North American Survey (NAS) and Hôpital Saint Louis (SLH). Observed actuarial cumulative incidence curves for SCC (step functions) and spline-smoothed estimates (smooth curves); shaded regions show 95% point-wise confidence intervals (CI). Curves in NAS and SLH indicate the cumulative incidence of SCC expected if the competing risks of non-SCC death could be removed and the hazard of development of SCC remained unchanged. From Ref. 12.

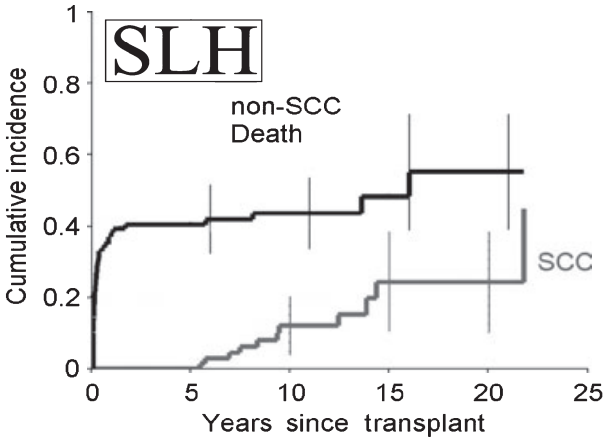

Fig. 5. Cumulative incidence of development of SCC (grey line) and non-SCC death (black line), by years since BMT, and 95% CIs at selected years. Data are from the Hôpital Saint Louis (SLH). Note the high mortality in the first 6 months following BMT, and the 5-year lag time before the first SCC appeared. From Ref. 12.

the high early mortality rate and also reduce the high rate of late-onset SCC. Literature reports of a variety of transplant regimens exemplify the problems. In the last 5 yr there have been more than 30 articles describing transplants in FA, but only seven of these included more than five patients treated with one specific protocol. It seems reasonable to suggest that collaboration by FA transplant centers using a single protocol might be informative with regard to testing variables in the regimens used for high-risk patients (i.e. those receiving transplants from donors other than HLA-matched siblings). In the data from the Paris cohort, the high early mortality rate was 7% per month. It would only take 25 high-risk patients, all transplanted with a single new protocol, to significantly reduce the early death rate by more than 2-fold. Since acute graft vs. host disease correlated with late onset HNSCC, the same number of patients might show a 7-fold significant reduction in this complication.

If FA transplant centers cannot agree on collaborative investigation of single protocols, it will take longer to determine whether a new protocol is better than any chosen previous standard, such as the Paris regimen. It would still be helpful to pool raw data, both retrospectively and prospectively, and to include both published and unpublished cases in a registry in order to do meta-analyses of individual results. Although recent short-term results from several centers do look promising, pooling of efforts will enable earlier determination of effective changes or elimination of deleterious modifications in SCT approaches.

Recommendations for hematologic monitoring of patients with FA include obtaining complete blood counts every 4 months or more often as needed and annual bone marrow examinations. The latter include aspirates for morphology, biopsies for cellularity, and cytogenetics with regard to development of bone marrow clones. Cancer surveillance targets the organs that are at risk. The oral cavity and pharynx should be examined at least yearly in untransplanted patients age 10 or above, or at any age following transplant. Monitoring should be done by physicians with expertise in head and neck cancer, and nasolaryngoscopy with a fiberoptic instrument should be included whenever possible. The presence of liver tumors may be detected by elevations in liver enzymes (followed every 3–4 months in patients on androgens and annually in others) and changes in liver imaging, usually annual ultrasound examinations. Skin cancer should be monitored with annual dermatologic inspection. For females, gynecologic examinations should begin at age 16 or menarche, whichever is first.

Management of leukemia or solid tumors in FA patients is complicated because of side effects due to defects in DNA repair in normal tissues. Choices of chemotherapy are limited to those agents that act by modalities other than DNA damage; radiation may result in substantial side effects in some patients (19). Until better therapies are identified, surveillance to find neoplasms while they are still small is the most prudent approach. Consideration should be given to future trials with vaccines against human papilloma virus to reduce the risk of gynecologic and possibly head and neck SCC. Additional strategies for investigation of the health of patients with FA are described on our web site (20).

References

1. Alter BP. Cancer in Fanconi Anemia, 1927–2001. Cancer 2003: 97: 425–440.
2. Kutler DI, Singh B, Satagopan J et al. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). Blood 2003: 101: 1249–1256.
3. Joenje H, Patel KJ. The emerging genetic and molecular basis of Fanconi Anaemia. Nat Rev Genet 2001: 2: 446–459.
4. Meetei AR, Levitus M, Xue Y, et al. X-linked inheritance of Fanconi Anemia complementation group B. Nat Genet 2004: 36: 1219–1224.
5. Levitus M, Rooimans MA, Steltenpool J, et al. Heterogeneity in Fanconi Anemia: evidence for two new genetic subtypes. Blood 2004: 103: 2498–2503.
6. Howlett NG, Taniguchi T, Olson S, et al. Biallelic inactivation of BRCA2 in Fanconi Anemia. Science 2002: 297: 606–609.
7. Garcia-Higuera I, Taniguchi T, Ganesan S, et al. Interaction of the Fanconi Anemia proteins and BRCA1 in a common pathway. Mol Cell 2001: 7: 249–262.
8. Alter BP. Inherited bone marrow failure syndromes. In: Nathan DG, Orkin SH, Look AT, Ginsburg D, eds. Nathan and Oski's Hematology of Infancy and Childhood. 6th edn. Philadelphia, PA: WB Saunders, pp. 280–365.
9. Faivre L, Guardiola P, Lewis C, et al. Association of complementation group and mutation type with clinical outcome in Fanconi Anemia. Blood 2000: 96: 4064–4070.
10. Rosenberg PS, Huang Z-G, Alter BP. Individualized risks of first adverse events in patients with Fanconi Anemia. Blood 2004: 104: 350–355.
11. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi Anemia. Blood 2003: 101: 822–826.
12. Rosenberg PS, Socie G, Alter BP, Gluckman, E. Risk of head and neck squamous cell cancer and death in transplanted and untransplanted patients with Fanconi Anemia. Blood 2005: 105: 67–73.
13. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's Anemia and non-fanconi's conditions. Am J Hematol 2004: 77: 257–267.
14. Alter BP, Caruso JP, Drachtman RA, Uchida T, Elghetany MT. Fanconi's Anemia: myelodysplasia as a predictor of outcome. Ca Genet Cytogenet 2000: 117: 125–131.
15. Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1973–1998. National Cancer Institute, Bethesda MD, http://seercancer.gov/csr/1975-2002.
16. Owen J, Frohnmayer L, Eiler, ME Fanconi Anemia: Standards for Clinical Care, 2nd edn. Eugene, OR: Fanconi Anemia Research Fund, Inc., 2005.
17. Hermsen MAJA, Xie Y, Rooimans MA, et al. Cytogenetic characteristics of oral squamous cell carcinomas in Fanconi Anemia. Familial Cancer 2001: 1: 39–43.
18. Soares MF, Machuca TN, Filho PRB, et al. Early presentation of squamous cell carcinoma after bone marrow transplantation in a boy with Fanconi Anemia. J Bras Patol Med Lab 2004: 40: 1–6.
19. Alter BP. Radiosensitivity in Fanconi's Anemia patients. Radiother Oncol 2002: 62: 345–347.
20. http://www.marrowfailure.cancer.gov.